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Correction to: Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies

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Following the original article's publication [1] the authors asked for the correction of Fig. 2, since the names of the disease genes [*GCH1* and *PCBD1*] in the figure published did not match the listed diseases [AR-GTPCHD and PCDD]. The correct Fig. 2 is shown below:

In the context of the manuscript correction and in order to match the text content, the words "apart from DHPRD" should be removed from the second row and second column of Table 4, as shown below:

The original article can be found online at https://doi.org/10.1186/s13023-020-01379-8.

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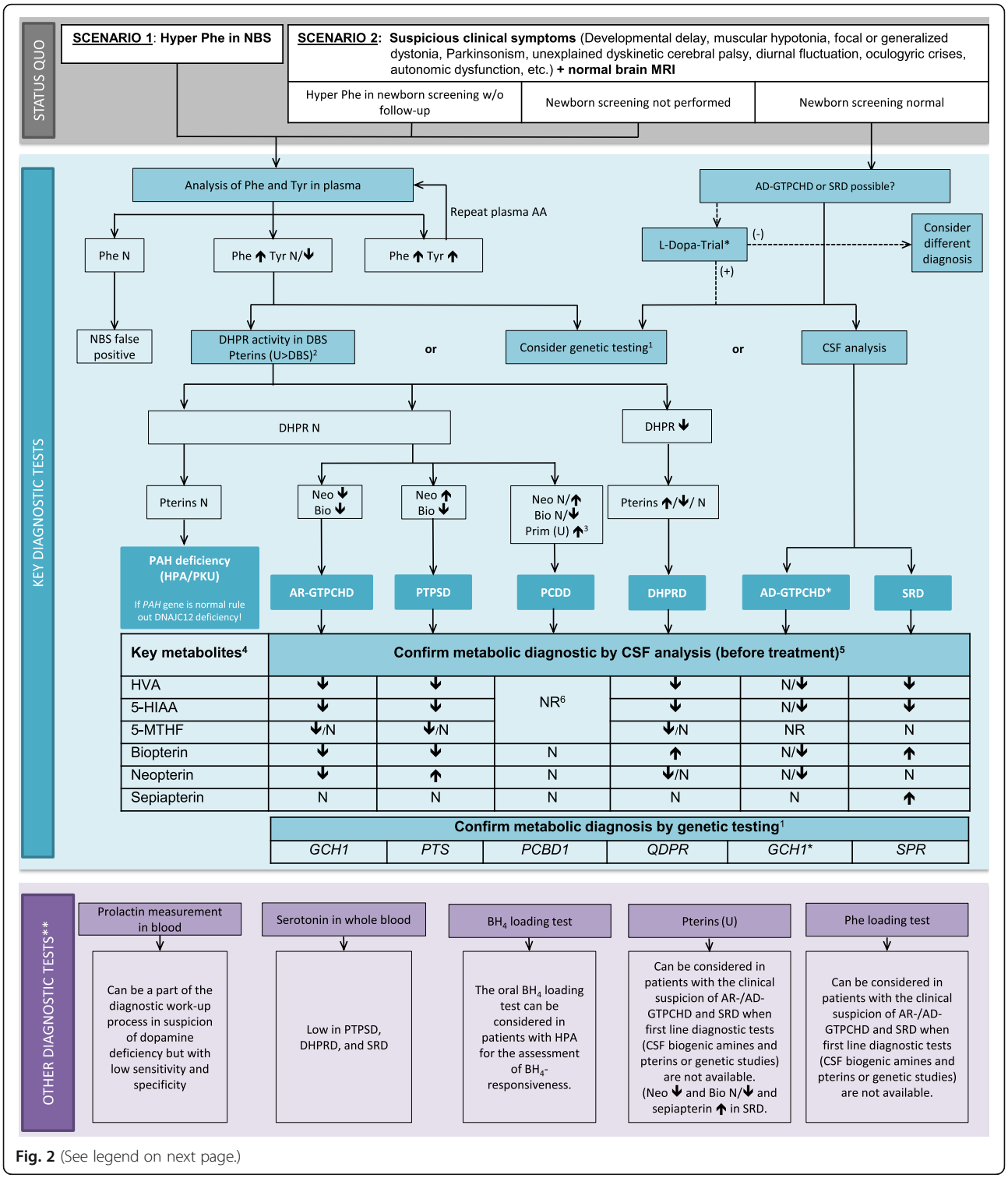

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Diagnostic flowchart for differential diagnosis of BH_4Ds with and without HPA. [1]Consider genetic HPA workup depending on availability and financial resources. The gene panel should include the *QDPR, GCH1, PTS PCBD1, SPR* genes as well as *DNAJC12*. For *GCH1*, consider MLPA if Sanger sequencing is negative. [2]The analysis in urine is more sensitive than in DBS and pathological patterns suggestive for PCDD and SRD can only be detected in urine but not in DBS. [3]Primapterin measurement in urine is only elevated in PCDD. [4]Aminoacids in CSF are not required for diagnosis of BH_4Ds. [5]CSF analysis should always include standard measurements (cell count, proteins, glucose and lactate). [6]Recommendation against measurements of HVA, 5-HIAA, 5-MTHF, and pterins in CSF in the case of PCDD. (*) A diagnostic L-Dopa trial should be limited to children with symptoms suggestive of dopa-responsive dystonia or to situations where biochemical and genetic diagnostic tools are not available. If the diagnostic L-Dopa trial is positive but the results of CSF biochemical and/or molecular genetic testing are not compatible with AD-GTPCHD or SRD, further aetiologies for dopa responsive dystonia should be considered (e.g. juvenile parkinsonism (PARK2gene)). (**) Can be considered if available. See text for more detailed information. Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-MTHF, 5-methyltetrahydrofolate; AA: amino acids; AD−/AR- GTPCHD: guanosine triphosphate cyclohydrolase I deficiency; BH_4, tetrahydrobiopterin; Bio: biopterin; CSF: cerebrospinal fluid; DBS: dry blood spot; DHPR: q-dihydropteridine reductase; DHPRD, dihydropteridine reductase deficiency; HVA, homovanillic acid; MRI, magnetic resonance imaging; N: normal; NBS: newborn screening; Neo: neopterin; NR: not reported; PAH: phenylalanine hydroxylase; Phe: phenylalanine; PKU: phenylketonuria; Prim: primapterin; PTPSD, 6-pyruvoyltetrahydropterin synthase deficiency; SRD: sepiapterin reductase deficiency; Tyr: tyrosine; u: urine; (+) = positive effect; (−) = no or no clear effect

Table 4 Recommended drugs and doses for BH_4 disorders

	Disorder	Starting dose	Doses	Target dose	Maximum dose	Management suggestion	Comment
First line treatments							
Phe-reduced diet	All BH_4D with HPA					Titrate Phe restriction according to Phe levels in DBS or plasma	Follow PKU national treatment recommendations Use either Phe reduced diet or Sapropterin dihydrochloride to control Phe levels
Sapropterin dihydrochloride	All BH_4D with HPA	2-5 mg/kg BW/day	Divided in 1–3 doses/day	5–10 mg/kg BW/day	20 mg/kg BW/day	Titrate dose according to Phe levels in DBS or plasma	Follow PKU national treatment recommendations Use either Phe reduced diet or Sapropterin dihydrochloride to control Phe levels
L-Dopa/DC inhibitor (carbidopa/benserazide) 4:1	All BH_4D apart from PCDD	0.5 mg–1 mg/kg BW/day Dose recommendation relates to L-Dopa component!	Divided in 2–6 doses/day	AD-GTPCHD: 3–7 mg/kg BW/day All other BH_4D: 10 mg/kg BW/day or maximally tolerated dosage Dose recommendation relates to L-Dopa component!	Depending on clinical symptoms. Some patients need more than 10 mg/kg BW/day for resolving clinical symptoms	Increase 0.5–1 mg/kg BW/day per week Follow BW adaption until the BW of 40 kg. After 40 kg adjust depending on clinical symptoms Consider analysis of CSF HVA for dose adjustment	In young infants at least as many dosages as meals would be ideal (usually 5–6 /day)
5-Hydroxytryptophan (5-HTP)	All BH_4D apart from AD-GTPCHD and PCDD	1–2 mg/kg BW/day	Divided in 3–6 doses/day	Published target dose recommendations are highly variable 5-HTP doses are usually lower than L-Dopa doses		Titrate slowly (1–2 mg/kg BW/day per week) depending on clinical picture and side effects Consider analysis of CSF 5HIAA for dose finding	5-HTP should follow L-Dopa/DCI treatment initiation Always in combination with a peripheral decarboxylase inhibitor (for example by simultaneous application with L-Dopa/DC inhibitor)
Folinic acid	In DHPRD and all BH_4D with low 5-MTHF in CSF		Divided in 1–2 doses/day	10–20 mg/day		No titration needed Consider analysis of CSF 5MTHF for dose finding	
Second line treatments							
Pramipexole[a] (Dopamine agonist)	All BH_4D apart from PCDD	3.5–7 μg/kg/BW/day (base) 5–10 μg/kgBW/day (salt) Note: Distinction in salt and base content! (see product insert)	Divided in 3 equal doses/day	Titrate to clinical Symptoms	75 μg/kg BW/day (3.3 mg/d base / 4 mg/d salt)	Increase every 7 days by 5 μg/kg BW/d	
Bromocriptine[a] (Dopamine agonist)	All BH_4D apart from PCDD	0.1 mg/kg BW/day	Divided in 2–3 doses/day	Titrate to clinical Symptoms	0.5 mg/kg/d (or 30 mg/d)	Increase every 7 days by 0.1 mg/kg BW/d	
Rotigotine[a] (transdermal dopamine agonist)	All BH_4D apart from PCDD	2 mg/day		Titrate to clinical Symptoms	8 mg/day	Increase weekly by 1 mg	Children > 12 years Exchange patch every 24 h
Selegiline[a] (MAO B inhibitor)	All BH_4D apart from PCDD	0.1 mg/kg BW/day	Divided in 2 (–3) doses/day	Titrate to clinical Symptoms	0.3 mg/kg/d (or 10 mg/d)	Increase every 2 weeks by 0.1 mg/kg BW/d	Can cause sleep disturbances – morning and afternoon or lunchtime dosage is possible ATTENTION: orally disintegrating preparation needs much less dosage because the first-pass effect of the liver is avoided

Table 4 Recommended drugs and doses for BH_4 disorders *(Continued)*

	Disorder	Starting dose	Doses	Target dose	Maximum dose	Management suggestion	Comment
Third line treatments							
Trihexyphenidyl[a] (Anticholinergic drugs)	All BH_4D apart from PCDD	< 15 kg: start 0.5–1 mg/day > 15 kg: start 2 mg/day	< 15 kg: in 1 dose > 15 kg: in 2 doses	Effective dose highly variable (6–60 mg) Titrate to clinical Symptoms	Maximum dose: < 15 kg BW 30 mg/day > 15 kg BW 60 mg/d	Increase every 7 days by 1–2 mg/d in 2–4 doses/d	Consider side effects: like dry mouth, dry eyes, blurred vision (mydriasis), urine retention, constipation.
Entacapone[a] (COMT inhibitor)	All BH_4D apart from PCDD	200 mg (adult)			Up to 2.000 mg		In many countries licensed only for adults. Comedication with L-Dopa/DC inhibitor Consider reduction of concomitant L-Dopa supplementation (10–30%)
Sertaline[a] (SSRI)	All BH_4D apart from PCDD	6–12 years: 25 mg/day in 1 dose > 12 years: 50 mg/day in 1 dose	6–12 years: in 1 dose > 12 years: in 1 dose	Children 50 mg/day	50 mg/day < 12 years 200 mg/day > 12 years	6–12 years: increase after 7 days to 50 mg/day in 1 dose > 12 years 50 mg/day in 1 dose	Don't stop treatment suddenly Note: Elevated risk of serotonin syndrome (SS) or malignant neuroleptic syndrome (MNS) when used with drugs impacting serotonergic pathway (e.g. 5-HTP, MAO inhibitors)
Melatonin[a]	All BH_4D apart from PCDD	0.01–0.03 mg/kg/day			5–8 mg/day		Slow release preparation for sleep-maintenance insomnia available in some countries

Please note: The doses given are in a range typically used and have been published. In individual patients, some adjustment may be necessary depending on symptom response and side effects

[a]The evaluated literature did not provide BH_4D specific treatment dose recommendations for this drug. The listed doses, therefore, indicate treatment recommendations from Summary of Product Characteristics (SmPC) or neurotransmitter related publications (e.g. [119])

Abbreviations: *5-HIAA* 5-hydroxyindoleacetic acid, *5-HTP* 5-hydroxytryptophan, *5-MTHF* 5- methyltetrahydrofolate, *HVA* Homovanillic acid, *AD-GTPCHD* Autosomal-dominant guanosine triphosphate cyclohydrolase I deficiency, *BH_4D* Tetrahydrobiopterin deficiency, *BW* Body weight, *COMT* Catechol-O-methyl transferase, *CSF* Cerebrospinal fluid, *DBS* Dry blood spot, *DC* Decarboxylase, *DCI* Decarboxylase inhibitor, *DHPRD* Dihydropteridine reductase deficiency, *L-Dopa* L-3,4-dihydroxyphenylalanine, *MAO B* Monoamine oxidase B, *PCDD* Pterin-4-alpha-carbinolamine dehydratase deficiency, *Phe* Phenylalanine, *PKU* Phenylketonuria, *SSRI* Selective serotonin reuptake inhibitor

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